



## warfarin sensitivity

Warfarin sensitivity is a condition in which individuals have a low tolerance for the drug warfarin. Warfarin is an anticoagulant, which means that it thins the blood, preventing blood clots from forming. Warfarin is often prescribed to prevent blood clots in people with heart valve disease who have replacement heart valves, people with an irregular heart beat (atrial fibrillation), or those with a history of heart attack, stroke, or a prior blood clot in the deep veins of the arms or legs (deep vein thrombosis).

Many people with warfarin sensitivity take longer than normal to break down (metabolize) warfarin, so the medication is in their body longer than usual and they require lower doses. These individuals are classified as "slow metabolizers" of warfarin. Other people with warfarin sensitivity do not need as much drug to prevent clots because their clot forming process is already slower than average and can be inhibited by low warfarin doses. If people with warfarin sensitivity take the average dose (or more) of warfarin, they are at risk of an overdose, which can cause abnormal bleeding in the brain, gastrointestinal tract, or other tissues, and may lead to serious health problems or death.

Warfarin sensitivity does not appear to cause any health problems other than those associated with warfarin drug treatment.

### Frequency

The prevalence of warfarin sensitivity is unknown. However, it appears to be more common in people who are older, those with lower body weights, and individuals of Asian ancestry.

Of the approximately 2 million people in the U.S. who are prescribed warfarin annually, 35,000 to 45,000 individuals go to hospital emergency rooms with warfarin-related adverse drug events. While it is unclear how many of these events are due to warfarin sensitivity, the most common sign is excessive internal bleeding, which is often seen when individuals with warfarin sensitivity are given too much of the medication.

### Genetic Changes

Many genes are involved in the metabolism of warfarin and in determining the drug's effects in the body. Certain common changes (polymorphisms) in the *CYP2C9* and *VKORC1* genes account for 30 percent of the variation in warfarin metabolism due to genetic factors. Polymorphisms in other genes, some of which have not been identified, have a smaller effect on warfarin metabolism.

The *CYP2C9* gene provides instructions for making an enzyme that breaks down compounds including steroids and fatty acids. The *CYP2C9* enzyme also breaks down certain drugs, including warfarin. Several *CYP2C9* gene polymorphisms can decrease the activity of the *CYP2C9* enzyme and slow the body's metabolism of warfarin. As a result, the drug remains active in the body for a longer period of time, leading to warfarin sensitivity.

The *VKORC1* gene provides instructions for making a vitamin K epoxide reductase enzyme. The *VKORC1* enzyme helps turn on (activate) clotting proteins in the pathway that forms blood clots. Warfarin prevents (inhibits) the action of *VKORC1* and slows the activation of clotting proteins and clot formation. Certain *VKORC1* gene polymorphisms decrease the amount of functional *VKORC1* enzyme available to help activate clotting proteins. Individuals develop warfarin sensitivity because less warfarin is needed to inhibit the *VKORC1* enzyme, as there is less functional enzyme that needs to be suppressed.

While changes in specific genes, particularly *CYP2C9* and *VKORC1*, affect how the body reacts to warfarin, many other factors, including gender, age, weight, diet, and other medications, also play a role in the body's interaction with this drug.

## **Inheritance Pattern**

The polymorphisms associated with this condition are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to result in warfarin sensitivity. However, different polymorphisms affect the activity of warfarin to varying degrees. Additionally, people who have more than one polymorphism in a gene or polymorphisms in multiple genes associated with warfarin sensitivity have a lower tolerance for the drug's effect or take even longer to clear the drug from their body.

## **Other Names for This Condition**

- coumadin sensitivity
- warfarin response

## **Diagnosis & Management**

These resources address the diagnosis or management of warfarin sensitivity:

- Food and Drug Administration Medication Guide  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/009218s116lbl.pdf#page=32](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009218s116lbl.pdf#page=32)
- Genetic Testing Registry: Warfarin response  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/CN078029/>
- MedlinePlus Drugs & Supplements: Warfarin  
<https://medlineplus.gov/druginfo/meds/a682277.html>

- My46 Trait Profile  
<https://www.my46.org/trait-document?trait=Warfarin%20sensitivity&parent=Medication%20Response&type=profile>
- PharmGKB  
<https://www.pharmgkb.org/guideline/PA166104949>
- WarfarinDosing.org  
<http://warfarindosing.org/Source/Home.aspx>

These resources from MedlinePlus offer information about the diagnosis and management of various health conditions:

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>
- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>

## **Additional Information & Resources**

### MedlinePlus

- Drugs & Supplements: Warfarin  
<https://medlineplus.gov/druginfo/meds/a682277.html>
- Encyclopedia: Deep Venous Thrombosis  
<https://medlineplus.gov/ency/article/000156.htm>
- Health Topic: Bleeding  
<https://medlineplus.gov/bleeding.html>
- Health Topic: Blood Thinners  
<https://medlineplus.gov/bloodthinners.html>

### Genetic and Rare Diseases Information Center

- Warfarin sensitivity  
<https://rarediseases.info.nih.gov/diseases/12639/warfarin-sensitivity>

### Educational Resources

- American Society of Hematology: Antithrombotic Therapy  
<http://www.hematology.org/About/History/50-Years/1523.aspx>
- Disease InfoSearch: Warfarin response  
<http://www.diseaseinfosearch.org/Warfarin+response/9469>
- My46 Trait Profile  
<https://www.my46.org/trait-document?trait=Warfarin%20sensitivity&parent=Medication%20Response&type=profile>
- Orphanet: Susceptibility to bleeding due to warfarine treatment  
[http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=240997](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=240997)
- StopAfib.org: Gene Test Improves Use of Coumadin (warfarin) for Stroke Prevention in Atrial Fibrillation  
<http://www.stopafib.org/newsitem.cfm/NEWSID/247/genetic%20testing%20improves%20Coumadin%20%28warfarin%29%20use/gene%20test%20helps%20atrial%20fibrillation%20stroke%20prevention>
- The Internet Stroke Center: Intracerebral Hemorrhage  
<http://www.strokecenter.org/patients/about-stroke/intracerebral-hemorrhage/>

### Patient Support and Advocacy Resources

- National Blood Clot Alliance  
<https://www.stoptheclot.org/>
- National Stroke Association  
<http://www.stroke.org/>

### Genetic Testing Registry

- Warfarin response  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/CN078029/>

### ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22warfarin+sensitivity%22+OR+%22coumadin+sensitivity%22+OR+%22warfarin+dosing%22>

### Scientific articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28warfarin+sensitivity%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

## OMIM

- COUMARIN RESISTANCE  
<http://omim.org/entry/122700>

## Sources for This Summary

- Ferder NS, Eby CS, Deych E, Harris JK, Ridker PM, Milligan PE, Goldhaber SZ, King CR, Giri T, McLeod HL, Glynn RJ, Gage BF. Ability of VKORC1 and CYP2C9 to predict therapeutic warfarin dose during the initial weeks of therapy. *J Thromb Haemost*. 2010 Jan;8(1):95-100. doi: 10.1111/j.1538-7836.2009.03677.x. Epub 2009 Oct 30.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/19874474>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3718044/>
- Flockhart DA, O'Kane D, Williams MS, Watson MS, Flockhart DA, Gage B, Gandolfi R, King R, Lyon E, Nussbaum R, O'Kane D, Schulman K, Veenstra D, Williams MS, Watson MS; ACMG Working Group on Pharmacogenetic Testing of CYP2C9, VKORC1 Alleles for Warfarin Use. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. *Genet Med*. 2008 Feb;10(2):139-50. doi: 10.1097/GIM.0b013e318163c35f.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/18281922>
- King CR, Deych E, Milligan P, Eby C, Lenzini P, Grice G, Porche-Sorbet RM, Ridker PM, Gage BF. Gamma-glutamyl carboxylase and its influence on warfarin dose. *Thromb Haemost*. 2010 Oct;104(4):750-4. doi: 10.1160/TH09-11-0763. Epub 2010 Aug 5.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/20694283>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2949522/>
- Krishna Kumar D, Shewade DG, Lorient MA, Beaune P, Balachander J, Sai Chandran BV, Adithan C. Effect of CYP2C9, VKORC1, CYP4F2 and GGCX genetic variants on warfarin maintenance dose and explicating a new pharmacogenetic algorithm in South Indian population. *Eur J Clin Pharmacol*. 2014 Jan;70(1):47-56. doi: 10.1007/s00228-013-1581-x. Epub 2013 Sep 10.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/24019055>
- Lund K, Gaffney D, Spooner R, Etherington AM, Tansey P, Tait RC. Polymorphisms in VKORC1 have more impact than CYP2C9 polymorphisms on early warfarin International Normalized Ratio control and bleeding rates. *Br J Haematol*. 2012 Jul;158(2):256-61. doi: 10.1111/j.1365-2141.2012.09150.x. Epub 2012 May 10.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/22571356>
- Moyer TP, O'Kane DJ, Baudhuin LM, Wiley CL, Fortini A, Fisher PK, Dupras DM, Chaudhry R, Thapa P, Zinsmeister AR, Heit JA. Warfarin sensitivity genotyping: a review of the literature and summary of patient experience. *Mayo Clin Proc*. 2009 Dec;84(12):1079-94. doi: 10.4065/mcp.2009.0278. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/19955245>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2787394/>

- Perera MA, Cavallari LH, Limdi NA, Gamazon ER, Konkashbaev A, Daneshjou R, Pluzhnikov A, Crawford DC, Wang J, Liu N, Tatonetti N, Bourgeois S, Takahashi H, Bradford Y, Burkley BM, Desnick RJ, Halperin JL, Khalifa SI, Langae TY, Lubitz SA, Nutescu EA, Oetjens M, Shahin MH, Patel SR, Sagreiya H, Tector M, Weck KE, Rieder MJ, Scott SA, Wu AH, Burmester JK, Wadelius M, Deloukas P, Wagner MJ, Mushiroda T, Kubo M, Roden DM, Cox NJ, Altman RB, Klein TE, Nakamura Y, Johnson JA. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. *Lancet*. 2013 Aug 31;382(9894):790-6. doi: 10.1016/S0140-6736(13)60681-9. Epub 2013 Jun 5.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/23755828>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3759580/>
- Saleh MI. Clinical Predictors Associated With Warfarin Sensitivity. *Am J Ther*. 2015 Mar 27. [Epub ahead of print]  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/25830869>
- Scott SA, Patel M, Martis S, Lubitz SA, van der Zee S, Yoo C, Edelmann L, Halperin JL, Desnick RJ. Copy number variation and warfarin dosing: evaluation of CYP2C9, VKORC1, CYP4F2, GGCX and CALU. *Pharmacogenomics*. 2012 Feb;13(3):297-307. doi: 10.2217/pgs.11.156. Epub 2011 Dec 21.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/22188360>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3292047/>
- van der Zee SA, Halperin JL. Anticoagulant therapy: warfarin sensitivity genotyping closer to clinical practice. *Nat Rev Cardiol*. 2010 Oct;7(10):549-50. doi: 10.1038/nrcardio.2010.126.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/20865027>

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